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The first principle of voltage gated ion channel and the general probability of circuit probability theory

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Abstract

A five-anchor model is provided to describe the physical working procedure of an individual ion channel. It provide the first principle for ion channel behavior: which is the polarity change of each anchor is induced by electron transition independently. Thus, the long off kenetics of neural stimulation by optogenetics, the stochastic gating pattern of single ion channel under DC voltage, the refractory period of action potential and the nerve conductance block, which are well observed for years in many studies, can be directly explained by this model. Meanwhile, as one part of the general Circuit-Probability theory [17], this model expand the probability calculation from a single equation, which is applied for the Circuit-Probability theory in our previous study, to a general form, which is a set of quantized operation.

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Introduction

Since the discovery of ion channel in 1952 [1], the research of ion channel is always the most essential issue for neuroscience. Starting from the famous Hodgkin–Huxley model (H-H model), people try building lots of phenomenological and mathematical models to explain and study the unique properties of all kinds of ion channels [2-10]. But unfortunately, the stochastic gating pattern of single ion channel [11-12] is contradictory with the deterministic nature of the H-H model, which is the cornerstone of the whole neuroscience, jeopardizing the correctness of its further development. Meanwhile, in the circuit-probability (C-P) theory developed in our previous study [13], the probability calculus equation also indicate the deep connection between the ion channel gating and quantum mechanics. Therefore, it seems that a new and more elementary ion channel model involving the quantum mechanism is inevitable.

In this study, a new ion channel model, called five-anchor model, is proposed. This model is built based on a hypothesis of the first principle of the protein beam in the ion channel: the polarity of the protein beam can be changed by electron transition. Then the behaviors and properties of ion channel in not only electrical stimulation, but also the optical stimulation, which is known as optogenetics, can be directly obtained from this model. Meanwhile, this model is consistent with our previous C-P theory. In this study, the probability calculus equation is amended and expanded to a more general scenario, thus called a general probability for differentiation with the probability calculus in C-P theory.

Five-anchor model

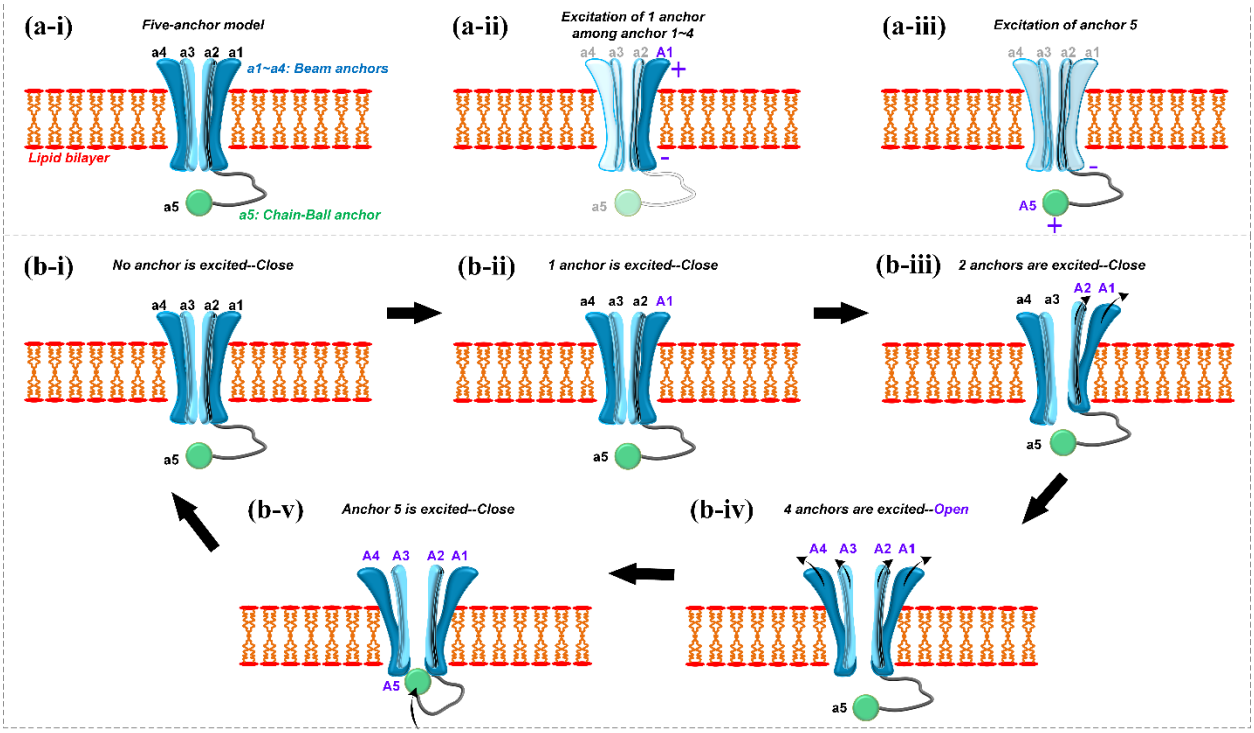

Figure 1. Five-anchor model of the ion channel (a) Structure of an ion channel and excitation states of beam anchors and the chain-ball anchor: (i) a1 to a4 refer to four beam anchors and a5 refers to the chain ball anchor, the lower case refers to the unexcited state; (ii) 1 anchor among beam anchors is excited, its polarity is changed, with a positive top end and a negative bottom end, the upper case refers to excited state; (iii) The chain-ball anchor is excited, its polarity is changed, the ball is positive charged and the chain is negative charged, the upper case refers to excited state; (b) A common operation procedure of the

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ion channel gating: (i) no anchor is excited, the ion channel is closed; (ii) 1 beam anchor is excited, the ion channel is closed; (iii) 2 beam anchors are excited and repel with each other, making these two anchors separate and lift up, but the channel is still closed; (iv) All four beam anchors are excited and repel with each other, making them all separate and lift up. The ion channel is open; (v) The chain-ball anchor is excited. The positive charged ball will be attracted to the negative charged bottom end of the beam anchors.

Physical working procedure of the ion channel

The five-anchor model describes a basic physical working procedure of an individual ion channel. Then based on the physical working procedure, a mathematical description can be directly obtained.

A typical biological structure of an individual ion channel is shown in Figure 1(a-i), with four protein beams and a chain-ball structure. All these four protein beams and the chain-ball structure are simplified as anchors to control the gating of the ion channel. The four protein beams are named as beam anchor (a1 to a4) while the chain-ball structure is named as chain-ball anchor (a5). An essential point to be emphasized here is that we do not specify the exact type the of the ion channel since this basic model can be applied for any kinds of ion channel. The only differences for various kinds of ion channels are the number of protein beams and with or without the chain-ball structure.

Then with a certain external excitation, these anchors can be excited by electron transition. Here we assume that an electron in one anchor can be excited from a low energy level to a high energy level, resulting in a polarity change of the anchor. For a1 to a4, the excitation will make the top end positive charged and bottom end negative charged, as shown in Figure 1(a-ii). For a5, the excitation will make the ball positive charged and the chain negative charged, as shown in Figure 1(a-iii). Here the anchors with unexcited and excited states are indicated with lower case and upper case, respectively. The essential point to be emphasized here is that the excitation for each anchor is independent with other anchors. It means how the state of one anchor changes (for example: from excited to unexcited; from unexcited to excited) is only determined by its current state and the external excitation, not affected by the statuses of other anchors.

Then a typical gating procedure for an action potential generation is shown in Figure 1(b). At the initial step, all 5 anchors are unexcited, thus the ion channel is closed (Figure 1(b-i)). Then a first beam anchor is excited with a polarity change, but nothing happen and the ion channel is still closed (Figure 1(b-ii)). Then a second anchor is excited with a polarity change. Since both two excited anchors are of the same polarity, they will repel with each, making these two anchors separate and lift up (Figure 1(b-ii)). But at this step, the ion channel is still closed. Only when all four beam anchors are excited and repel with each other, the ion channel is open (Figure 1(b-iv)). Then the chain-ball anchors is excited. Since the ball is positive charged, it will be attracted to the negative charged bottom end of excited beam anchors and block the ion channel (Figure 1(b-v)). At this step, the ion channel is closed. Then after a certain duration, all anchors recover to the unexcited state (Figure 1(b-i)), the ion channel is closed.

Mathematical description

Since the anchor excitation is induced by electron transition, the mathematical description can also directly obtained from this physical mechanism.

Excitation by electric field

For the electron transition induced by electric field, there will also be a threshold strength. **Thus as an observation, there will be a threshold voltage required for exciting the anchors [16].**

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Here define the event of excitation of the anchor $\boldsymbol{n}$ as $\boldsymbol{A_n}$, and the recovery of the anchor $\boldsymbol{n}$ as $\boldsymbol{a_n}$. Considering all quantum events follow the exponential distribution, then the probability of $\boldsymbol{A_n}$ is

$$\boldsymbol{P(A_n) = 1 - e^{-\int \lambda_{An}(V(t))dt}};$$

The function of $\boldsymbol{\lambda_{An}}$ is:

$$\boldsymbol{\lambda_{An}(V(t)) = \alpha_n \times \frac{1}{e^{\frac{\beta_n}{|V(t)-V_{T_n}|}}-1}};$$

Here $\boldsymbol{V_{T_n}}$ refers to the threshold voltage of the anchor $\boldsymbol{n}$. $\boldsymbol{\alpha_n}$ and $\boldsymbol{\beta_n}$ are physical parameters determined by the molecular structure of the anchor $\boldsymbol{n}$. $\boldsymbol{V(t)}$ refers to the effective voltage upon the ion channel, which can be introduce by any sources such as action potential, electrical stimulation, magnetic stimulation and even acoustic stimulation [17]. This equation follows the same form as Planck's law since the electron transition is a quantum event.

Then the probability of $\boldsymbol{a_n}$, the event of recovery of anchor $\boldsymbol{n}$, is

$$\boldsymbol{P(a_n) = 1 - e^{-\int \lambda_{an}dt} = 1 - e^{-\lambda_{an}\times t}};$$

Here $\boldsymbol{\lambda_{an}}$ is a constant, not affected by the external voltage. It means the recovery of the electron from a higher energy to a lower energy cannot be controlled by external input. It is a spontaneous procedure. Also in quantum mechanism, this recovery still can be controlled by other photon, called stimulated emission [18], but this mechanism is neglected here. Thus

$$\boldsymbol{\lambda_{an} \propto \alpha_n};$$

The physical meaning of this formula is that if the electron transition is more likely to happen (the energy level difference is lower), it will take a longer time for it to recover from the high energy level to low energy level. This effect on the chain-ball anchor (a5) will be very special. Once a5 is excited and block the ion channel, this ion channel cannot be open by external stimulation again until a5 recovers to the unexcited state. **The observation of this phenomenon is called refractory period [1].**

Since all parameters involved are determined by the molecular structure, we can assume the beam anchors (a1~a4) share the same parameters, which are different from those of chain-ball anchor (a5). Meanwhile, considering the function of chain-ball anchor is to close the ion channel when the amplitude of the action potential exceeds the sufficient level, so a5 should be triggered at a relatively higher voltage. Thus the threshold voltage of a5 ($\boldsymbol{V_{T_5}}$) should be higher than that of beam anchors.

With the above equations, with an exact external applied voltage waveform, the gating procedure of a single ion channel can be modelled.

The opening of an ion channel (event $\boldsymbol{O}$) can be expressed as:

$$\boldsymbol{O = A_1 \cap A_2 \cap A_3 \cap A_4 \cap a_5};$$

The close of an ion channel (event $\boldsymbol{C}$) is:

$$\boldsymbol{C = a_1 \cup a_2 \cup a_3 \cup a_4 \cup A_5};$$

Previously, people already observed the stochastic gating pattern of a single ion channel [11]. Here we can reproduced this gating pattern as shown in Figure 2.

As can be seen, with increasing the DC voltage (from V=-1 to V=-7), the ion channel will open more frequently. However the ion channel can never keep an always open state since the beam anchors can spontaneously recover to unexcited state. But with a higher voltage, the close duration will be shorter

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because the recovered beam anchor can be quickly excited again and make the ion channel open. Meanwhile, there will be some very short open periods. This is the situation that one beam anchor is recovered to unexcited state immediately after the excitation of another recovered beam. This very short open period can always happen and is not controllable.

Then if further increase the voltage, the chain-ball anchor is excited to close the ion channel. Thus as can be seen, the channel is now close more frequently. But no matter how high is the DC voltage, there always have some short open periods since a5 will spontaneously recover and enable the ion channel to open.

The above description is exactly the observation of gating pattern of a single ion channel by DC voltage [11-12].

However, in our theory, the voltage $\boldsymbol{V(t)}$ does not necessarily be a DC voltage. Actually the gating pattern of any voltage can be modelled. If a high frequency AC voltage with different amplitude is applied, the gating pattern will be similar as shown in the Figure 2.

Thus here we can directly get the prediction for nerve conductance block. Nerve conductance block is a phenomenon observed when a continuous electrical input is applied on a nerve. This continuous electrical input can block the neural signal propagation.

Now it is easier to understand this phenomenon with Figure 2. When a voltage is high enough to keep exciting the beam anchors, which is the case when V=-7, the ion channel is always recruited, resulting in two effects. First, the ion channel cannot response to the coming action potential since all beam anchors are keeping triggering. Then the frequent opening of ion channel will result in a depletion of the ion concentration difference, which is essential to the activation of action potential. Thus for this case of nerve conductance block, there will be a serious fatigue after the blocking. However, if further increase the voltage applied for the blocking test, the gating of the ion channel will change from frequently open to frequently close because of the excitation of a5. So in this case, the ion channel also cannot response to the coming action potential. But since the ion channel is always closed, there will be no consumption of the ion concentration difference, result in no fatigue after the blocking test. **The above description is exactly the observed phenomenon of the nerve conductance block [19].**

Moreover, it is easy to predict that the voltage or current required for DC nerve conductance block will be much higher than that of AC nerve conductance block. As explain by our previous study [13], the neural circuit is of a parallel RLC circuit configuration. Thus its voltage response to AC input will be much higher than that of the DC input. **That is why a higher DC input is required to meet the threshold voltage for triggering the anchors.**

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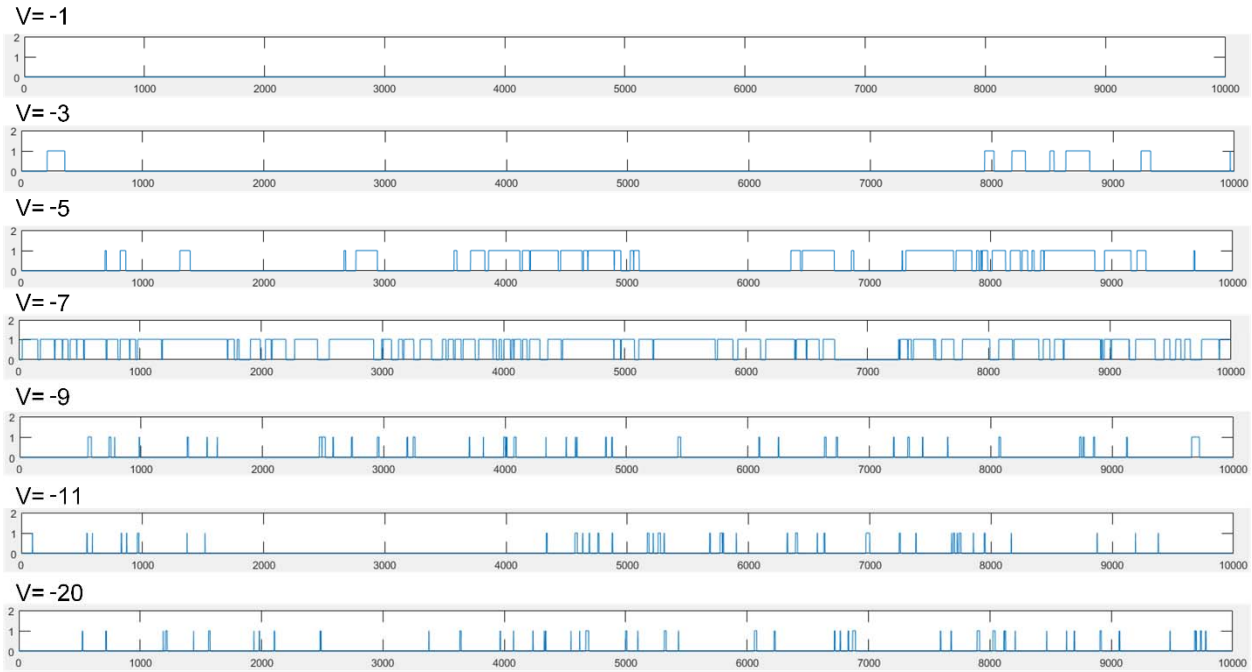

Figure 2. The gating pattern of a single ion channel with different DC voltage.

Excitation by photon

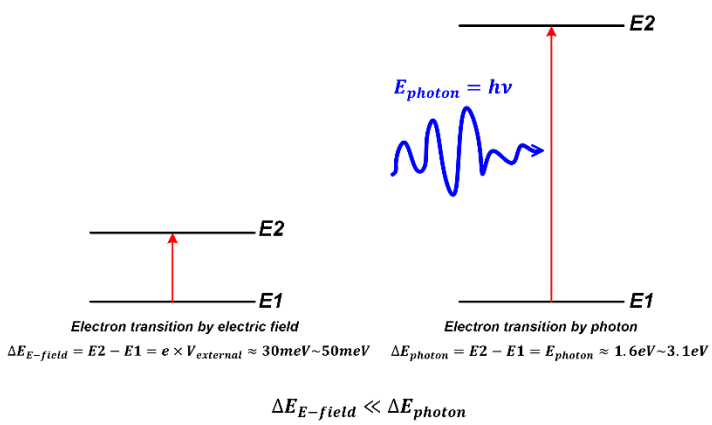

Figure 3 Comparison of the electron transition in electrical nerve stimulation and optical nerve stimulation.

The electron transition induced by photon is well-known as photoelectric effect. To induce an electron transition from a low energy level to a high energy level, the energy of the photon should be higher than the energy level difference. So only the light whose frequency is higher than a threshold can excite the electron transition then trigger the opening an ion channel. This is what happens in neural stimulations by optogenetics. Although the voltage gated ion channels do not have completely the same structure as that of light gated ion channels, the fundamental working mechanism, which is the electron transition, should be the same. Thus just as the criteria for photoelectric effect, the frequency of the light should be higher than a threshold to activate the light-gated ion channel [14].

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A circumstantial evidence to support this opinion comes from the excited state lifetime difference between electrical nerve stimulation and optical nerve stimulation as shown in Figure 3.

For the electrical nerve stimulation, the typical external voltage required is ranging from 30 mV to 50 mV. The energy to be absorbed by the electron to have transition from lower energy level to high energy level can be estimated as:

$$\Delta E_{E-field} = E2 - E1 = e \times V_{external} \approx 30\ meV \sim 50\ meV$$

However, the light required for nerve stimulation by optogenetics is normally within the range of visible light, whose wavelength is from 400nm to 760nm. Thus the energy delivered to the electron can be estimated as:

$$\Delta E_{photon} = E2 - E1 = E_{photon} = h\nu \approx 1.6\ eV \sim 3.1\ eV$$

As can be seen, compared with the electrical stimulation, the energy required for optical stimulations is much higher, resulting in a much longer excited state lifetime. It means the electron can be kept in the high energy level for a longer time before the spontaneous emission happens. So it takes a longer time for each anchor to recover from the excited state. Before the recovery of all anchors, the ion channel cannot be stimulated again. **So as an observation, neural stimulation by optogenetics normally has a very long "off kenetics", ranging from 4 ms to 29 mins, while ion channel stimulated by electric field can normally recover within 1 ms[15].**

Summary

In summary, a five-anchor model is provided to describe the physical working procedure of an individual ion channel. It provide the first principle for ion channel behavior: which is the polarity change of each anchor is induced by electron transition independently. Thus, the long off kenetics of neural stimulation by optogenetics, the stochastic gating pattern of single ion channel under DC voltage, the refractory period of action potential and the nerve conductance block, which are well observed for years in many studies, can be directly explained by this model. Meanwhile, as one part of the general Circuit-Probability theory [17], this model expand the probability calculation from a single equation, which is applied for the Circuit-Probability theory in our previous study, to a general form, which is a set of quantized operation.

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